
Pfizer Ireland Pharmaceuticals

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Office of Licensing, Climate & Resource Use,
Environmental Protection Agency,
PO Box 3000,
Johnstown Castle Estate,
Co. Wexford.
Y35 W821.

4th April 2019

Licence Register No. P0153-05

Dear Sir/Madam,

Pfizer Ireland Pharmaceuticals (PIP) wish to inform the Agency that it is proposed to conduct pilot and full-scale scale pharmaceutical manufacturing development with the Active Pharmaceutical Ingredient (API) Tolterodine Tartrate in the Technical Services Area (Technology Innovation Centre) at the Newbridge facility for a period of approximately 6 months commencing in April/May 2019. The purpose of this work is to assess the suitability for potential future full scale production of this product at the site.

PIP can confirm that this product is consistent with current site operations and manufacturing processes and will not result in any change in the overall emissions generated on site nor does it represent any significant change to on-site activities.

A Safety Data Sheet for the Tolterodine Tartrate API, which is non-hormonal in nature, is presented in Appendix 1. A revised Table G.1 'Details of Process related Raw Materials, Intermediates, Products, etc., used or generated on the site' which includes this API is presented in Appendix 2 (Material Ref. N^o 1633 highlighted in red text). PIP also presents for information purposes other compounds have been added to this table as per Ref. No 1634 – 1642 (highlighted in red text). These materials (lubricants, fire extinguishing agent, anti-corrosive agent, oil) are similar in nature to other materials currently used on site. For this reason it is considered that the introduction of these materials will not result in any change in the overall emissions generated on site nor do they represent any significant change to on-site activities.

Air emissions from the Technology Innovation Centre will be vented through appropriate main atmospheric emission points at this building location (Emission Point Reference No. A2-25, A2-26). As there is no change in the licenced quantity of active dust expected to be discharged, and the emission characteristics from the trial processes will be similar to those already licensed under Licence Register No. P0153-05, these trials will have no additional impact on the receiving environment. Annual monitoring of Main Emissions to Atmosphere as per the requirements of *Schedule C.1.2 Monitoring of Emissions to Air* of Licence Register No. P0153-05 will be implemented to confirm this assertion.



All liquid (including all wastewater containing API) and solid waste will be collected, consigned off-site as a hazardous waste and treated using the current approved waste management contractor Indaver Ireland Ltd.

If you have any queries about the approach outlined above, please do not hesitate in contacting me.

Yours sincerely,

A handwritten signature in blue ink that reads "E Molyneaux".

Dr. Edward Molyneaux
Environmental, Health & Safety Lead



Appendix 1
Safety Data Sheet



Tolterodine Tartrate



SAFETY DATA SHEET

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1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND THE COMPANY/UNDERTAKING

Product Identifier

Material Name: Tolterodine L-Tartrate

Trade Name: Not established
Compound Number: PNU-0200583E
Synonyms: Tolterodine Tartrate
Chemical Family: Not determined

Relevant Identified Uses of the Substance or Mixture and Uses Advised Against

Intended Use: Pharmaceutical active for the treatment of overactive bladder

Details of the Supplier of the Safety Data Sheet

Pfizer Global Supply
Pfizer Inc
235 East 42nd Street
New York, NY 10017
1-800-879-3477

Pfizer Ltd
Ramsgate Road
Sandwich, Kent
CT13 9NJ
United Kingdom
+00 44 (0)1304 616161

Emergency telephone number:
CHEMTREC (24 hours): 1-800-424-9300
Contact E-Mail: pfizer-MSDS@pfizer.com

Emergency telephone number:
International CHEMTREC (24 hours): +1-703-527-3887

2. HAZARDS IDENTIFICATION

Classification of the Substance or Mixture

GHS - Classification

Reproductive Toxicity: Category 2
Acute aquatic toxicity: Category 2
Chronic aquatic toxicity: Category 2

US OSHA Specific - Classification

Physical Hazard: Combustible Dust

EU Classification:

EU Indication of danger: Toxic to Reproduction: Category 3
N - Dangerous for the environment

EU Risk Phrases:

R63 - Possible risk of harm to the unborn child.
R51/53 - Toxic to aquatic organisms. May cause long-term adverse effects in the aquatic environment.

Label Elements

Signal Word: Warning
Hazard Statements: H361d - Suspected of damaging the unborn child
H411 - Toxic to aquatic life with long lasting effects
May form combustible dust concentrations in air

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Precautionary Statements: P201 - Obtain special instructions before use
P273 - Avoid release to the environment
P281 - Use personal protective equipment as required
P308 + P313 - IF exposed or concerned: Get medical attention/advice
P391 - Collect spillage
P405 - Store locked up

Supplemental Hazards: Strong dust explosion characteristic.
Very high sensitivity to ignition.



Other Hazards No data available
Australian Hazard Classification (NOHSC): Hazardous Substance. Non-Dangerous Goods.

Note: This document has been prepared in accordance with standards for workplace safety, which requires the inclusion of all known hazards of the product or its ingredients regardless of the potential risk. The precautionary statements and warning included may not apply in all cases. Your needs may vary depending upon the potential for exposure in your workplace.

3. COMPOSITION / INFORMATION ON INGREDIENTS

Hazardous

Ingredient	CAS Number	EU EINECS/ELINCS List	EU Classification	GHS Classification	%
Tolterodine L-Tartrate	124937-52-6	Not Listed	Repr. Cat. 3;R63 N;R51/53	Repr. 2 (H361d) Aquatic Acute 2 (H401) Aquatic Chronic 2 (H411)	100

Additional Information: Ingredient(s) indicated as hazardous have been assessed under standards for workplace safety.

For the full text of the R phrases and CLP/GHS abbreviations mentioned in this Section, see Section 16

4. FIRST AID MEASURES

Description of First Aid Measures

Eye Contact: Flush with water while holding eyelids open for at least 15 minutes. Seek medical attention immediately.

Skin Contact: Remove contaminated clothing. Flush area with large amounts of water. Use soap. Seek medical attention.

Ingestion: Never give anything by mouth to an unconscious person. Wash out mouth with water. Do not induce vomiting unless directed by medical personnel. Seek medical attention immediately.

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Inhalation: Remove to fresh air and keep patient at rest. Seek medical attention immediately.

Most Important Symptoms and Effects, Both Acute and Delayed

Symptoms and Effects of Exposure: For information on potential signs and symptoms of exposure, See Section 2 - Hazards Identification and/or Section 11 - Toxicological Information.
Medical Conditions Aggravated by Exposure: None known

Indication of the Immediate Medical Attention and Special Treatment Needed

Notes to Physician: None

5. FIRE FIGHTING MEASURES

Extinguishing Media: Extinguish fires with CO₂, extinguishing powder, foam, or water.

Special Hazards Arising from the Substance or Mixture

Hazardous Combustion Products: Emits toxic fumes of carbon monoxide and nitrogen oxide.

Fire / Explosion Hazards: Strong dust explosion characteristic. Very high sensitivity of a dust cloud to ignition, based on minimum ignition energy.

Advice for Fire-Fighters

During all fire fighting activities, wear appropriate protective equipment, including self-contained breathing apparatus.

6. ACCIDENTAL RELEASE MEASURES

Personal Precautions, Protective Equipment and Emergency Procedures

Personnel involved in clean-up should wear appropriate personal protective equipment (see Section 8). Minimize exposure.

Environmental Precautions

Place waste in an appropriately labeled, sealed container for disposal. Care should be taken to avoid environmental release.

Methods and Material for Containment and Cleaning Up

Measures for Cleaning / Collecting: Contain the source of the spill if it is safe to do so. Collect spilled material by a method that controls dust generation. Avoid use of a filtered vacuum to clean spills of dry solids, due to the potential for electrostatic discharge and the strong dust explosion potential and very high sensitivity to ignition. Clean spill area thoroughly.

Additional Consideration for Large Spills: Non-essential personnel should be evacuated from affected area. Report emergency situations immediately. Clean up operations should only be undertaken by trained personnel.

7. HANDLING AND STORAGE

Precautions for Safe Handling

Ground and bond all bulk transfer equipment. Avoid open handling. Minimize dust generation. All conductive elements of the system that contact the dry substance should be properly bonded and grounded and equipped with proper explosion relief or suppression systems. This material should not be flowed through nonconductive ducts or pipes because of the potential for electrostatic discharge ignition. Restricting the use of high resistivity materials, such as plastics, should be considered. Avoid inhalation and contact with skin, eye, and clothing. Use local exhaust ventilation or perform work under fume hood/fume cupboard. When handling, use appropriate personal protective equipment (see Section 8). Wash hands and any exposed skin after removal of PPE. Releases to the environment should be avoided. Review and implement appropriate technical and procedural waste water and waste disposal measures to prevent occupational exposure or environmental releases. Potential points of process emissions of this material to the atmosphere should be controlled with dust collectors, HEPA filtration systems or other equivalent controls. Refer to Section 12 - Ecological Information, for information on potential effects on the environment.

Conditions for Safe Storage, Including any Incompatibilities

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Storage Conditions: Store at room temperature in properly labeled containers. Keep away from heat, sparks and flames.
Specific end use(s): Pharmaceutical active

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Control Parameters

Tolterodine L-Tartrate

Pfizer OEL TWA-8 Hr: 25µg/m³

Analytical Method: Analytical method available. Contact Pfizer Inc for further information.

Exposure Controls

Engineering Controls: Engineering controls should be used as the primary means to control exposures. Use process containment, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits.

Personal Protective Equipment: Refer to applicable national standards and regulations in the selection and use of personal protective equipment (PPE).

Hands: Wear impervious gloves as minimum protection.

Eyes: Wear safety glasses as minimum protection.

Skin: Wear impervious protective clothing when handling this compound.

Respiratory protection: If the applicable Occupational Exposure Limit (OEL) is exceeded, wear an appropriate respirator with a protection factor sufficient to control exposures to below the OEL.

9. PHYSICAL AND CHEMICAL PROPERTIES

Physical State:	Crystalline powder	Color:	White
Odor:	No data available.	Odor Threshold:	No data available.
Molecular Formula:	C ₂₂ H ₃₁ N O . C ₄ H ₆ O ₆	Molecular Weight:	457.58

Solvent Solubility: Soluble: Methanol. Slightly soluble: Ethanol.

Water solubility: 12 mg/mL

Water Solubility: No data available

pH: No data available.

Melting/Freezing Point (°C): 206-212

Boiling Point (°C): No data available.

Partition Coefficient: (Method, pH, Endpoint, Value)

Tolterodine L-Tartrate

Predicted Log P 5.24

Decomposition Temperature (°C): No data available.

Evaporation Rate (Gram/s): No data available

Vapor Pressure (kPa): No data available

Vapor Density (g/ml): No data available

Relative Density: No data available

Viscosity: No data available

Flammability:

Autoignition Temperature (Solid) (°C): No data available

Flammability (Solids): No data available

Flash Point (Liquid) (°C): No data available

Upper Explosive Limits (Liquid) (% by Vol.): No data available

Lower Explosive Limits (Liquid) (% by Vol.): No data available

Dust Explosivity:

Max. Explosion Pressure (bar): 78

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Max. Rate of Pressure Rise (bar/sec):	8750
Kst Value (bar*m/s):	233
St Class:	2
Min. Ignition Energy (mJ):	0.10 J
Min. Explosion Concentration (g/m ³):	0.045 oz./cu.ft.
Electrostatic Risk:	
Charge Relaxation Time:	623 Seconds
Resistivity (ohm-m):	
Powder:	3.59E15

10. STABILITY AND REACTIVITY

Reactivity:	No data available
Chemical Stability:	Stable under normal conditions of use.
Possibility of Hazardous Reactions	
Oxidizing Properties:	No data available
Conditions to Avoid:	Fine particles (such as dust and mists) may fuel fires/explosions.
Incompatible Materials:	As a precautionary measure, keep away from strong oxidizers
Hazardous Decomposition Products:	No data available

11. TOXICOLOGICAL INFORMATION

Information on Toxicological Effects

Short Term:	Accidental ingestion may cause effects similar to those seen in clinical use.
Long Term:	Animal studies have shown a potential to cause adverse effects on the fetus.
Known Clinical Effects:	May cause effects similar to those seen in clinical use including dry mouth, blurred vision, constipation, and upset stomach.

Acute Toxicity: (Species, Route, End Point, Dose)

Tolterodine L-Tartrate

Mouse Oral LD 50 > 200 mg/kg

Acute Toxicity Comments: A greater than symbol (>) indicates that the toxicity endpoint being tested was not achievable at the highest dose used in the test.

Irritation / Sensitization: (Study Type, Species, Severity)

Tolterodine L-Tartrate

Skin Irritation Rabbit Non-irritating
Skin Sensitization - GPMT Guinea Pig No effect

Repeated Dose Toxicity: (Duration, Species, Route, Dose, End Point, Target Organ)

Tolterodine L-Tartrate

26 Week(s) Mouse Oral 10 mg/kg/day NOEL None identified
52 Week(s) Dog Oral 0.5 mg/kg/day NOEL None identified

Reproduction & Development Toxicity: (Duration, Species, Route, Dose, End Point, Effect(s))

Tolterodine L-Tartrate

Reproductive & Fertility-Females Mouse Oral 20 mg/kg/day NOEL No effects at maximum dose

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11. TOXICOLOGICAL INFORMATION

Reproductive & Fertility-Males	Mouse	Oral	30 mg/kg/day	NOAEL	No effects at maximum dose
Embryo / Fetal Development	Mouse	Oral	20 mg/kg/day	NOAEL	Embryotoxicity, Teratogenic

Genetic Toxicity: (Study Type, Cell Type/Organism, Result)

Tolterodine L-Tartrate

Bacterial Mutagenicity (Ames)	<i>Salmonella</i> , <i>E. coli</i>	Negative
<i>In Vivo</i> Chromosome Aberration	Human Lymphocytes	Negative
<i>In Vivo</i> Micronucleus	Mouse	Negative

Carcinogenicity: (Duration, Species, Route, Dose, End Point, Effect(s))

Tolterodine L-Tartrate

Not specified	Mouse	Oral	30 mg/kg/day	Maximally Tolerated Dose	Not carcinogenic
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Carcinogen Status: Not listed as a carcinogen by IARC, NTP or US OSHA.

12. ECOLOGICAL INFORMATION

Environmental Overview: Toxic to aquatic organisms. May cause long term adverse effects in the aquatic environment.

Toxicity:

Aquatic Toxicity: (Species, Method, End Point, Duration, Result)

Tolterodine L-Tartrate

<i>Daphnia magna</i> (Water Flea)	OECD	LC50	48 Hours	1.7 mg/L
<i>Pseudokirchneriella subcapitata</i> (Green Alga)	EC50	72 Hours	20 mg/L	

Persistence and Degradability: No data available

Bio-accumulative Potential:

Partition Coefficient: (Method, pH, Endpoint, Value)

Tolterodine L-Tartrate

Predicted	Log P	5.24
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Mobility in Soil: No data available

13. DISPOSAL CONSIDERATIONS

Waste Treatment Methods:

Dispose of waste in accordance with all applicable laws and regulations. Member State specific and Community specific provisions must be considered. Considering the relevant known environmental and human health hazards of the material, review and implement appropriate technical and procedural waste water and waste disposal measures to prevent occupational exposure and environmental release. It is recommended that waste minimization be practiced. The best available technology should be utilized to prevent environmental releases. This may include destructive techniques for waste and wastewater.

14. TRANSPORT INFORMATION

The following refers to all modes of transportation unless specified below.

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Not regulated for transport under USDOT, EUADR, IATA, or IMDG regulations.

15. REGULATORY INFORMATION

Safety, Health and Environmental Regulations/Legislation Specific for the Substance or Mixture

Canada - WHMIS: Classifications

WHMIS hazard class:

Class D, Division 2, Subdivision A



Tolterodine L-Tartrate

CERCLA/SARA 313 Emission reporting

Not Listed

California Proposition 65

Not Listed

EU EINECS/ELINCS List

Not Listed

16. OTHER INFORMATION

Text of R phrases and GHS Classification abbreviations mentioned in Section 3

Reproductive toxicity-Cat.2; H361d - Suspected of damaging the unborn child

Hazardous to the aquatic environment, acute toxicity-Cat.2; H401 - Toxic to aquatic life

Hazardous to the aquatic environment, chronic toxicity-Cat.2; H411 - Toxic to aquatic life with long lasting effects

Xn - Harmful

N - Dangerous for the environment

R63 - Possible risk of harm to the unborn child.

R51/53 - Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

Data Sources: Pfizer proprietary drug development information. Publicly available toxicity information.

Reasons for Revision: Updated Section 1 - Identification of the Substance/Preparation and the Company/Undertaking.

Revision date: 19-Mar-2015

Product Stewardship Hazard Communication

Prepared by: Pfizer Global Environment, Health, and Safety Operations

Pfizer Inc believes that the information contained in this Material Safety Data Sheet is accurate, and while it is provided in good faith, it is without warranty of any kind, expressed or implied. If data for a hazard are not included in this document there is no known information at this time.

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End of Safety Data Sheet



Appendix 2

Revised Table G.1

'Details of Process related Raw Materials, Intermediates, Products, etc., used or generated on the site'

Table G.1 (i): Details of Process related Raw Materials, Intermediates, Products, etc., used or generated on the site

Ref. N ^o or Code	Material/Substance ⁽¹⁾	CAS Number	Danger ⁽²⁾ Category	Amount Stored (tonnes)	Annual Usage (tonnes)	Nature of Use	R ⁽³⁾ - Phrase	S ⁽³⁾ - Phrase
1628	Coni-snap hard gelatin empty capsules 100 mg	N/A	Not a dangerous product	25	85	Excipient	-	-
1629	Coni-snap hard gelatin empty capsules 200 mg	N/A	Not a dangerous product	25	85	Excipient	-	-
1630	Celecoxib	169590-42-5	Toxic to reproduction, Category 2 Harmful	15	22.5	Active	R61, R53, R48/22 H360D, H373, H410	P201, P202, P281 P308 + P313, P260, P314, P405, P391, P273, P501
1631	ITI 007 (Active Material)	N/A	Acute Tox 4,	15	22.5	Active	R22 H303	P264, P301+P312, P330 P501
1632	Tofacitinib Citrate (Xeljanz)	540737-29-9	Acute Oral Toxicity: Category 4 Reproductive Toxicity: Category 1B	2	2	Active	H302, H360Df	P201, P264, P281, P308 + P313, P405.
1633	Tolterodine L-Tartrate (Detrol)	124937-52-6	Reproductive Toxicity: Category 2 Acute aquatic toxicity: Category 2 Chronic aquatic toxicity: Category 2	0.005	0.005	Active	R63, R51/53, H361d, H401, H411	P20, P273, P281, P308 + P313 P391, P405
1634	Inergen	124-38-9	Simple asphyxiant	0.2	-	Fire Extinguishing Agent	-	P9
1635	Foodmax AW	-	Not a dangerous product	0.025	0.003	Lubricant	R51/53	-
1636	Soraja FM 372	-	Not a dangerous product	0.025	0.003	Lubricant	-	-
1637	Shell Omala S2 G 680	91745-46-9	Not a dangerous product	0.025	0.003	Lubricant	-	-
1638	Klubersynth UHI 14- 31 1. 2,6-Di-tert-butyl-p-cresol 2. 2-(2-heptadec-8-enyl-2-imidazolin-1-yl)ethanol 3. (Z)-N-methyl-N-(1-oxo-9 octadecenyl)glycine	1. 128-37-0 2. 95-38-5 3. 110-25-8	Specific Target Organ Toxicity (Repeated Exposure) - Category 2	0.025	0.003	Lubricant	R52/53, R20, R22, R48/22, R34, R41, R38	-
1639	Neudos KI 75	-	Not a dangerous product	0.005	0.002	Anti-corrosive	-	-
1640	Klüberoil 4 UHI-1500N Spray 1. Butane 2. Isobutane 3. Propane 4. amine neutralized phosphoric acid ester of alkylated alcohols	1. 106-97-8 2. 75-28-5 3. 74-98-6 4. -	Extremely flammable	0.025	0.002	Lubricating spray	R12, R 36/38, R51/53	-
1641	Optileb GT 460 1. Amine phosphate 2. 2,6-ditert-butyl-p-cresol 3. N-Oleyl sarcosine	1. 80939-62-4 2. 128-37-0 3. 110-25-8	Dangerous	0.025	0.002	Gear lubricant	R52/53, R36/38, R51/53, R50/53, R41, R38, R20	S61
1642	WM100	-	Not a dangerous product	0.005	0.005	Vacuum pump oil	-	-

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- Notes:
- In cases where a material comprises a number of distinct and available dangerous substances, please give details for each component substance.
 - c.f. Article 2(2) of SI N^o 77/94
 - c.f. Schedules 2 and 3 of SI N^o 77/94

Table G.1(ii): Details of Process related Raw Materials, Intermediates, Products, etc., used or generated on the site

Ref. N ^o or Code	Material/ Substance ⁽²⁾	TA Luft Class 1, 2 or 3	Odour			EU Lists I and II (Tick and specify Group/Family Number)			
			Odourous Yes/No	Description	Threshold $\mu\text{g}/\text{m}^3$	Dangerous Substances Directive 76/464/EEC		Groundwater Directive 80/68/EEC	
						List I	List II +129 ⁽⁴⁾	List I	List II
1628	Coni-snap hard gelatin empty capsules 100 mg	-	No	-	-	Not classified	Not classified	Not classified	Not classified
1629	Coni-snap hard gelatin empty capsules 200 mg	-	No	-	-	Not classified	Not classified	Not classified	Not classified
1630	Celecoxib	-	No data available	No data available	No data available	4		4	
1631	ITI 007 (Active Material)	-	No	No data available	No data available	No data available	No data available	No data available	No data available
1632	Tofacitinib Citrate (Xeljanz)	-	No data available	No data available	No data available	No data available	No data available	No data available	No data available
1633	Tolterodine L-Tartrate (Detrol)		No data available	No data available	No data available	4	-	4	-
1634	Inergen	-	No	No data available	No data available	No data available	No data available	No data available	No data available
1635	Foodmax AW		No	No data available	No data available	4	-	4	-
1636	Soraja FM 372		No	No data available	No data available	8	-	8	-
1637	Shell Omala S2 G 680		Yes	Slight hydrocarbon	No data available	7	-	7	-
1638	Klübersynth UH1 14- 31		Yes	Characteristic	No data available	4	-	4	-
1639	Neudos KI 75		Yes	Characteristic	No data available	8	-	8	-
1640	Klüberoil 4 UH1-1500N Spray		Yes	Product specific	No data available	8	-	8	-
1641	Optileb GT 460		Yes	Mild	N/A	4	-	4	-
1642	WM100		Yes	Slight hydrocarbon.	No data available	No data available	No data available	No data available	No data available

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Notes (cont.):

4. The European Commission priority candidate list